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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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OPPEDAHL AND LARSON LLP
P O BOX 5068
DILLON, CO 80435-5068

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2005 and 30 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7,8,10-13,16,21-26,28-30 and 32* is/are pending in the application.

4a) Of the above claim(s) *7,8,10-12 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,12,13,16,25,26,28-30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The amendment filed May 11, 2005, which was retransmitted on May 30, 2005, is acknowledge and has been entered. Claims 4, 6, 17-20, 27, and 31 have been canceled. Claim 1 has been amended.

2. Claims 1-3, 5, 7, 8, 10-13, 16, 21-26, 28-30, and 32 are pending in the application. Claims 7, 8, 10, 11, and 21-24 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 29, 2002.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following Office action contains NEW GROUNDS of rejection.

5. Claims 1-3, 5, 12, 13, 16, 25, 26, 28-30, and 32 are currently under prosecution.

Response to Arguments

6. Applicant's arguments with respect to claims 1-3, 5, 12, 13, 16, 25, 26, 28-30, and 32 have been considered but are moot in view of the new ground(s) of rejection.

Response to Amendment

7. The amendment filed September 8, 2003 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "Representative,

non-limiting examples of cytoplasmic domains which may be employed in the present invention include the ζ-chain cytoplasmic domain, the CD28 cytoplasmic domain (particularly a fragment encoded **by bases including bases** 336 to 663 of CD28 cDNA), 41BB, CD40, ICOS and trance" (emphasis added). The amendment was apparently intended to correct an erroneous disclosure, since at page 6 the specification originally disclosed "a fragment spanning amino acids 336 to 663 *of CD28 cDNA*" (underlining and italics added for emphasis). As further described at page 15, the amplified fragment of a plasmid comprising a cDNA molecule encoding CD28, which was used to construct the expression vector encoding the exemplified chimeric receptor, encodes part of the extracellular domain, the transmembrane domain, and the cytoplasmic domain of CD28. Although at page 15 the specification discloses that this fragment corresponds to a segment of the cDNA that consists of *amino acids* 336 to 663, since the fragment is a nucleic acid molecule, it is necessarily comprised of nucleotides, not amino acids. Accordingly, it is believed that the originally filed specification would support an amendment to the specification at page 5, such that it reads, "(particularly a fragment encoded by a segment consisting of nucleotides 336 to 663 of CD28 cDNA)", but it is not so clear that it would support the present amendment because of an apparent difference in scope. A particular fragment encoded by bases including bases 336 to 663 of CD28 cDNA is any fragment encoded by a segment comprising nucleotides 336-663 of the cDNA; however, a fragment encoded by a polynucleotide sequence comprising this segment is not necessarily the same as a fragment encoded by the segment alone and the disclosure at page 15, once an appropriate correction has been made, would merely describe a particular fragment encoded by a segment consisting of nucleotides 336-663 of the cDNA molecule encoding CD28, which is contained within the plasmid "pbsCD28". The disclosure at page 15 would not describe a genus of particular fragments encoded by polynucleotide sequences comprising the specified segment.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Ground of Objection

Specification

8. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, there is a sequence, namely $(gly\text{-}ser_2)_5$, which is disclosed at page 10 (paragraph 2) of the specification, but not identified by a sequence identification number.

Applicant must provide appropriate amendment to the specification, inserting the required sequence identifier.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

9. The specification is objected to because of apparent erroneous disclosures at page 7, paragraph 2, and 15, paragraph 2. At page 7, the specification discloses a preferred CD28 moiety is one that spans *amino acids* 336 to 663 of CD28 cDNA; but a cDNA molecule is composed of nucleotides or basepair, not amino acids. At page 15, it discloses the segment of the cDNA encoding part of the extracellular, transmembrane and cytoplasmic domains of human CD28, which was amplified by PCR, consists of *amino acids* 336 to 663. The amplified segment consisted of nucleotides 336 to 663. Appropriate correction is required.

Claim Objections

10. Claims 12, 25, 26, and 28 are objected to because the claims are directed to peripheral blood lymphocytes transduced with and expressing a fusion receptor. To transduce a cell is to effect transduction, which is a term of art customarily meaning the transfer of genetic material (and its phenotypic expression) from one cell to another by viral infection; see, e.g., Stedman's Online Medical Dictionary, 27th Edition, which is available on the Internet at http://www.stedmans.com/. Accordingly, a cell is transduced with a vector encoding a fusion receptor but a cell is not transduced with a fusion receptor. Appropriate correction or rebuttal is required, but it is suggested that this issue be remedied by amending the claims to recite, for example, a peripheral blood lymphocyte transduced with an expression vector encoding a fusion receptor in accordance with claim 1 and expressing the fusion receptor.

11. Claim 5 is objected to because the claim recites the term "41-BB"; however, as evidenced by Hurtado et al. (of record), for example, the protein to which the claim is directed is designated 4-1BB. Appropriate correction is required.

New Grounds of Claim Rejections

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 12, 13, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

The claims are directed to a fusion protein comprising a member of a genus of "cytoplasmic domains", which are the cytoplasmic domain of a molecule that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor.

The specification includes a description of a few members of the genus of cytoplasmic domains to which the claims are directed, including, in particular, a cytoplasmic domain of the zeta chain of CD3, a cytoplasmic domain of CD28, and a cytoplasmic domain of 4-1BB. The specification discloses that additional, non-limiting examples of suitable cytoplasmic domains include CD40, ICOS and trance (page 6).

Although each of these proteins are proteins known to function as a transducer of a mammalian immune response in the presence of a costimulatory factor, they apparently share no structurally identifying feature, which serves to delineate them and other members of the genus of cytoplasmic domains to which the claims are directed from other proteins. Moreover, although each is to act as a transducer of a mammalian immune response in the presence of a costimulatory factor, each has a markedly different physiologic function. Therefore, given the structural disparity among the different members of the genus, which have been described, despite the fact that each acts as a transducer of a mammalian immune response in the presence of a costimulatory factor, these few members do not appear to adequately represent the genus as a whole, because the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of its members.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001)

states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

The mere description of a few members of the genus of "cytoplasmic domains", which are structurally and functionally different proteins, is not sufficient to meet the requirements of 35 USC § 112, first paragraph, since the genus embraces widely variant members and an adequate description of such cannot be achieved by describing members, which are not representative of the genus. As disclosed and claimed, the genus does not comprise members having a common, particularly identifying structural feature that correlates with a common functional feature shared by at least a substantial number of its members. As such, absent any of the factual evidence of an actual reduction to practice discussed above, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the

claimed genus said at least substantial number. Accordingly, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 103

14. Claims 1-3, 12, 13, 25, 26, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2 in view of U.S. Patent No. 5,538,866 A.

Claims 1-3 are drawn to a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds prostate-specific membrane antigen (PMSA) and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge. Claims 13, 29, and 30 are drawn to an expression vector comprising a polynucleotide sequence encoding such a fusion protein. Claims 12, 25, and 26 are drawn to peripheral blood lymphocytes transduced with such expression vectors and expressing such fusion proteins.

Both U.S. Patent Application Publication No. 2003/0077249 A1 (Bebbington et al.) and WO 97/23613 A2 (Bebbington et al.) teach peripheral blood lymphocytes transduced with an expression vector comprising a polynucleotide sequence encoding a fusion protein comprising a scFv that binds a tumor-associated antigen and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge. See the entire documents (e.g., Figure 1).

Neither U.S. Patent Application Publication No. 2002/0137697 A1 nor WO 97/23613 A2 expressly teach the scFv of the fusion protein binds PMSA.

U.S. Patent No. 5,538,866 A (Israeli et al.) teaches PMSA is a prostate tumor-associated antigen; see entire document (e.g., the abstract). Israeli et al. teaches antibodies that bind PMSA are therapeutically useful; see, e.g., column 6, lines 44-48;

and column 23, line 44, through column 24, line 6. Citing Eshhar et al. (*Br. J. Cancer Suppl.* 1990 Jul; 10: 27-29), Israeli et al. teaches the following:

> Antibodies of required specificity can also be cloned into T cells and by replacing the immunoglobulin domain of the T cell receptor (TcR); cloning in the desired MAb heavy and light chains; splicing the V_H and V_L gene segments with the constant regions of the .alpha. and .beta. TCR chains and transfecting these chimeric Ab/TcR genes in the patients' T cells, propagating these hybrid cells and infusing them into the patient (33). Specific knowledge of tissue specific antigens for targets and generation of MAb's specific for such targets will help make this a usable approach. Because the PSM antigen coding region provides knowledge of the entire coding region, it is possible to generate a number of antibodies which could then be used in combination to achieve an additive or synergistic anti-tumor action.

Accordingly, Israeli et al. suggests making and using chimeric T cell receptors that incorporate the anti-tumour specificity of a monoclonal antibody that binds PMSA, since hybrid T cells transfected with expression vectors encoding such chimeric T cell receptors could be infused into a patient as a means to direct the cytolytic activity of the T cells to prostate tumors in the patient.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have made peripheral blood lymphocytes transduced with an expression vector encoding a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds PMSA and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge, because Israeli et al. suggests making such hybrid T cells expressing such fusion proteins (i.e., chimeric T cell receptors) and Bebbington et al. teaches making peripheral blood lymphocytes transduced with an expression vector encoding such a fusion protein, which comprises a scFv that binds any tumor-associated antigen and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge. One ordinarily skilled in the art at the time of the invention would have been motivate to do so because the prior art teaches or suggests that transduced peripheral blood lymphocytes expressing such fusion proteins may be used therapeutically to treat prostate cancer.

15. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2 in view of U.S. Patent No. 5,538,866 A, as applied to claims 1-3, 12, 13, 25, 26, 29 and 30 above, and further in view of Lams et al. (*Hum. Gene Ther.* 1996 Aug 1; **7** (12): 1415-1422).

Claim 13 is drawn to an expression vector comprising a polynucleotide sequence encoding a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds prostate-specific membrane antigen (PMSA) and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge, which is packaged in gibbon ape leukemia virus envelope-pseudotyped virions.

U.S. Patent Application Publication No. 2003/0077249 A1 (Bebbington et al.), WO 97/23613 A2 (Bebbington et al.), and U.S. Patent No. 5,538,866 A teach that which is set forth above in the rejection of claims 1-3, 12, 13, 25, 26, 29 and 30 under 35 U.S.C. § 103.

In addition, Bebbington et al. teaches different methods for the introduction of the expression vector encoding the fusion protein into immune cells, including by transduction using a retrovirus. In U.S. Patent Application Publication No. 2003/0077249 A1, for example, Bebbington et al. discloses the use of such methodology at paragraph [0070].

However, neither Bebbington et al. nor U.S. Patent No. 5,538,866 A expressly teach packaging the expression vector in gibbon ape leukemia virus envelope-pseudotyped virions.

Lam et al. teaches gene-modified lymphocytes have a potential role in the therapy of cancer and discloses methodology for improved gene transfer into human lymphocytes using retroviruses that use the gibbon ape leukemia virus (GALV) envelope, as opposed to retroviruses that use the amphotropic envelope; see entire document (e.g., the abstract). Moreover, Lam et al. teaches their findings suggest that gene transfer into human T lymphocytes should be performed using such GALV

envelope-pseudotyped virions, as opposed to virions comprised of amphotropic envelope (abstract).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have packaged the expression vector in GALV envelope-pseudotyped virions in order to transduce human peripheral lymphocytes because Lam et al. teaches that such methodology should be used, as opposed to packaging the expression vector in virions that use the amphotropic envelope, because the latter methodology provides for less effective gene transfer. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to improve gene transfer into human lymphocytes.

16. Claims 5, 28, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2 in view of U.S. Patent No. 5,538,866 A, as applied to claims 1-3, 12, 13, 25, 26, 29 and 30 above, and further in view of Shuford et al. (*J. Exp. Med.* 1997 Jul 7; **186** (1): 47-55).

Claim 5 is drawn to a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds prostate-specific membrane antigen (PMSA) and a cytoplasmic domain of 4-1BB, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge. Claim 32 is drawn to an expression vector comprising a polynucleotide sequence encoding such a fusion protein. Claim 28 is drawn to peripheral blood lymphocytes transduced with such expression vectors and expressing such fusion proteins.

U.S. Patent Application Publication No. 2003/0077249 A1 (Bebbington et al.), WO 97/23613 A2 (Bebbington et al.), and U.S. Patent No. 5,538,866 A teach that which is set forth above in the rejection of claims 1-3, 12, 13, 25, 26, 29 and 30 under 35 U.S.C. § 103.

In addition, Bebbington et al. teaches chimeric receptors comprise any of several different proteins, including costimulatory proteins (e.g., CD2, CD28) that act to transduce a signal that results in the activation of immune cells. In U.S. Patent

Application Publication No. 2003/0077249 A1 (paragraph [0620]), for example, Bebbington et al. discloses:

> Besides the specific receptor chains specifically mentioned herein, the single chain Fv chimeras can be made by joining the scFv domain with any receptor or co-receptor chain having a similar function to the disclosed molecules, e.g., derived from granulocytes, B lymphocytes, mast cells, macrophages, etc. The distinguishing features of desirable immune cell trigger molecules comprise the ability to be expressed autonomously (i.e., as a single chain), the ability to be fused to an extracellular domain such that the resultant chimera is expressed on the surface of an immune cell into which the corresponding gene was genetically introduced, and the ability to take part in signal transduction programs secondary to encounter with a target ligand.

However, neither Bebbington et al. nor U.S. Patent No. 5,538,866 A expressly teach a fusion protein (i.e., chimeric receptor) comprised of the cytoplasmic domain of 4-1BB.

Shuford et al. teaches 4-1BB provides a costimulatory signals preferentially induce CD8+ T cell proliferation *in vitro* and *in vivo* and lead to the amplification *in vivo* of cytotoxic T cell responses; see entire document (e.g., the abstract). In this regard, Shuford et al. teaches costimulation through 4-1BB and CD28 are reciprocal in nature and complimentary to one another by activating individually CD8+ and CD4+ T cells, respectively (page 48, column 1). Shuford et al. teaches the 4-1BB-mediated preferential stimulation of CD8+ T cells *in vivo* has promoted the rejection of large established tumors (paragraph bridging columns at page 55).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have made peripheral blood lymphocytes transduced with an expression vector encoding a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds PMSA and a cytoplasmic domain of 4-1BB, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge, because Iraeli et al. suggests making such hybrid T cells expressing such fusion proteins (i.e., chimeric T cell receptors), Bebbington et al. teaches making peripheral blood lymphocytes transduced with an expression vector encoding such a fusion protein, which comprises a scFv that binds any tumor-associated antigen and the cytoplasmic domain of any costimulatory protein that acts to

transduce a signal that results in the activation of immune cells (e.g., a cytoplasmic domain of CD28), wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge, and Shuford et al. teaches the cytoplasmic domain of 4-1BB is a costimulatory protein that transduces a signal that preferentially results in the activation of CD8+ cytotoxic T cells, which promote the rejection of tumors. One ordinarily skilled in the art at the time of the invention would have been motivate to do so because the prior art teaches or suggests that transduced peripheral blood lymphocytes expressing such fusion proteins may be used therapeutically to treat prostate cancer.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-3, 12, 13, 25, 26, 29, and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1-5, 7-13, 15-20, 22-30, 32-38, 40-45, and 47-50 of copending Application No. 10/448,256 in view of U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2.

Claims 1-3 of the instant application are drawn to a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds prostate-specific membrane antigen (PMSA) and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge. Claims 13, 29, and 30 are drawn to an expression vector comprising a polynucleotide sequence encoding such a fusion protein. Claims 12, 25, and 26 are drawn to peripheral blood lymphocytes transduced with such expression vectors and expressing such fusion proteins.

In contrast, claims 1-5, 7-13, 15-20, 22-30, 32-38, 40-45, and 47-50 of copending Application No. 10/448,256 are drawn to nucleic acid molecules encoding chimeric T cell receptors (i.e., fusion proteins) comprising a scFv that binds PMSA, the intracellular (i.e., cytoplasmic) domain of the zeta chain of CD3, and a constimulatory signaling region comprising the intracellular domain of CD28. The copending claims do not describe nucleic acid molecules encoding such chimeric T cell receptors comprising an optional connector that directly or indirectly adjoins the scFv and the cytoplasmic domain of the zeta chain or the intracellular domain of CD28, which is or comprises a CD8 hinge. Furthermore, the copending claims are not specifically directed to expression vectors, or peripheral blood lymphocytes transduced with such expression vectors, or to the chimeric proteins encoded by the claimed nucleic acid molecules.

Both U.S. Patent Application Publication No. 2003/0077249 A1 (Bebbington et al.) and WO 97/23613 A2 (Bebbington et al.) teach peripheral blood lymphocytes transduced with an expression vector comprising a polynucleotide sequence encoding a fusion protein comprising a scFv that binds a tumor-associated antigen and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge. See the entire documents (e.g., Figure 1).

Given the claims of the copending application, in view of the teachings Bebbington et al., it would have been obvious to one ordinarily skilled in the art at the time of the invention to have made peripheral blood lymphocytes transduced with an expression vector encoding a fusion protein comprising a single-chain Fv antibody fragment of an antibody (scFv) that binds PMSA and a cytoplasmic domain of the zeta chain of CD3 or a cytoplasmic domain of CD28, wherein the scFv and the cytoplasmic domain are optionally adjoined by a connector comprising a CD8 hinge.

This is a provisional obviousness-type double patenting rejection.

19. Claims 1-3, 12, 13, 25, 26, 29, and 30 are directed to an invention not patentably distinct from claims 1-5, 7-13, 15-20, 22-30, 32-38, 40-45, and 47-50 of commonly assigned copending Application No. 10/448,256 in view of U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2. Specifically, for the reasons set forth above in the obviousness-type double patenting rejection, despite minor differences, in view of the prior art, the claimed subject matter of the copending application renders obvious the claimed subject matter of the instant application.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/448,256, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

20. Claims 1-3, 12, 13, 25, 26, 29, and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-13, 15-20, 22-30, 32-38, 40-45, and 47-50 of copending Application No. 10/448,465 in view of U.S. Patent Application Publication No. 2003/0077249 A1 or WO 97/23613 A2.

Because the claims of copending Application No. 10/448,465 are substantially the same as, or identical to the claims of copending Application No. 10/448,256, the claims of the former render the claims of the instant application obvious in view of the prior art for the same reasons the claims of the latter do so; see the above rejection of the claims over the latter application in view of the prior art.

This is a provisional obviousness-type double patenting rejection.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
September 13, 2005

Notice to Comply	Application No.	Applicant(s)	
	09/786,502	SADELAIN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct deficiency, Applicant is required to submit substitute copies of the Sequence Listing together with an amendment directing its entry and a statement that both copies are the same and include no new matter, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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